Continues Postoperative Analgesia: A Double-Blinded, Placebo-Controlled, Randomized Clinical Trial the Addition of a Small-Dose Ketamine Infusion to Tramadol Infusion

Ahmed Haki Ismael MBChB, DA, M.Sc.

Ali Hadi Muslih MBChB, FICMS

Abstract

Background: There are few data on combining ketamine with tramadol for continuous postoperative analgesia in humans. The hypothesis of adding ketamine to tramadol would improve analgesia after major and super-major surgery had been tested.

Method: In this double-blind, randomized, controlled trial, adult patients (n = 120) having elective major surgery were randomly assigned to a ketamine group (postoperative infusion at 0.1 mg / kg / h) or control group (equivalent volume/rate of normal saline). All patients received intra-operative tramadol 3 mg/kg and a tramadol infusion (0.2 mg / kg /h) for 48 h postoperatively.

Results: In the 0–24 h period, ketamine improved subjective analgesic efficacy ($P < 0.05$), was less sedating ($P < 0.05$), and required fewer physician interventions to manage severe pain ($P < 0.05$). The ketamine group had less pain at rest ($P < 0.05$) and with movement ($P < 0.05$) and required less additional analgesic (Diclofenac sodium) ($P < 0.05$) throughout the 48-h study period. Hallucinations were more common in ketamine patients, but other side effects were similar.

Conclusion: Small-dose ketamine was a useful addition to tramadol infusion after major and super-major surgery in continuous postoperative analgesia.

Key words: ***Ketamine infusion, Tramadol infusion, Postoperative continuous analgesia, Subjective analgesia efficacy (SAE)***

Introduction

This clinical trial demonstrated improved pain relief after major surgery by the addition of ketamine to IV tramadol infusion as continuous postoperative analgesia. Combining ketamine and tramadol improved analgesia, was reducing physician interventions to manage severe pain.

There are considerable data supporting the addition of ketamine to morphine for postoperative pain. [1-5]After major surgery, tramadol combined with morphine patient-controlled analgesia (PCA) was morphine-sparing and improved analgesia compared with morphine PCA alone [6] Human studies on the analgesic efficacy of combining ketamine and tramadol infusions are lacking. PCA ketamine/tramadol combinations have been compared with tramadol PCA alone in one small trial finding improved early postoperative analgesia. [7] Co-administration of ketamine and tramadol in mice achieved synergistic antinociception in a chemically-induced persistent pain model, but not in acute thermal or chemical pain models. [8]

Aim of the study

To show if there is an improvement in the (subjective analgesia efficacy - SAE) by infusing a small dose of ketamine, as an adjunct to tramadol infusion in continuous post operative analgesia.

Patients & Method

Patients were ASA physical status I–III; aged 19-75 yr. Exclusion criteria included chronic pain, chronic opioid usage, or any contraindication to tramadol, ketamine, NSAID or opiates. The ethical means had been taken into consideration, by avoiding any physical or psychological harm that may happen to the patients.

One hundred twenty adults having elective major surgery, were recruited to this double-blind, randomized, controlled trial. The recruited cases were general surgery (cholecystectomy, bowel resection, nephrectomy, renal stone, ureteric stone and prostatectomy), gynecological surgery (hysterectomy) and orthopedic surgery (open reduction with internal fixation) .The randomization of patient's allocation in each group was done by a special randomization table, by sorting numbers randomly in each group. The groups were labeled as group 1 and group 2, and the drugs which had been given to each group remained concealed until the end of data collection and analysis, in order to avoid bias as much as possible.

The Drugs prepared by an anesthetist, who had neither participated in data collection nor data analysis. The whole hospital staff was blinded from the contents of the solutions (matter of study). Study medications were prepared and transferred to the blinded anesthesiologist in the operating room who was responsible for data collection and analysis. The preparation and blinding was as follows:

1-Group 1(ketamine group) had received 0.3mg/kg B wt. ketamine (Syringe containing 2ml of solution and blinded and labeled as solution No.1) at anesthetic induction and a ketamine infusion (0.9% normal solution containing 500 mg ketamine, blinded and labeled as solution No.1).

2-Control group: An equivalent volume of normal saline (Syringe labeled as solution No.2) at induction of anesthesia followed by a normal saline infusion (Plain 0.9% normal saline

solution, labeled and blinded as solution No.2) at equivalent rate to maintain blinding.

Anesthetic technique

Standard anesthetic technique was used in all the patients. After securing intravenous line, monitoring gadgets were attached this included ECG, SPO_2 and noninvasive BP cuff. Baseline parameters were observed and recorded. Injection tramadol (2 mg/kg with maximum dose of 100 mg) was given IV 2 minutes before the induction of anesthesia in both the groups.

Induction and maintenance of anesthesia

In both the groups, injection of pancronium bromide (0.1 mg/kg body wt. as a loading dose) was given as a muscle relaxant before the administration of the induction dose of the intravenous anesthetic agent, (thiopentone sodium in a dose of 3-4 mg /kg b. wt.). Muscle relaxation was maintained with pancronium bromide of 1 mg increments each 25-30 minutes. Anesthesia was maintained with halothane and 100% oxygen.

Patients were ventilated with 100% oxygen via a facemask for 60-90 seconds with the help of Bain's circuit, and intubation was done with an appropriate size of cuffed endotracheal tube. Patients were ventilated with 100% oxygen with the application of IPPV set.

Reversal of relaxant effect

All the anesthetic drugs were stopped 5-7 minutes before the anticipated end of surgery. At the end of surgery, neuromuscular blockade was reversed with injection neostigmine 40 µg/kg body wt. and injection atropine 20 µg/kg body wt. which was given over 2-3 minutes period. Extubation was done when the patients were able to maintain rhythmic respiration and adequate tidal volume.

Diclofenac sodium was given to the patients in a dose of 1 mg/kg. B. wt (up to 75 mg) as an analgesic 5 minutes after discharging to the recovery room.

Tramadol infusion with solution No.1 infusion or solution No.2 infusion (matter of study) started 10 minutes after discharge from the operating room. The tramadol was prepared as 500 mg tramadol in 500 ml 0.9% normal saline.

The study's primary point was improvement in subjective analgesic efficacy (SAE) in which patients were asked, "How effective was your medication in relieving your pain over the last 24 h?" with responses: 1 = excellent, 2 = good, 3 = satisfactory, 4 = poor, and 5 = very poor. The (SAE) was intercepted by the blinded anesthesiologist who is responsible for the study at 24 and 48 hours postoperatively.

Pain scores by using verbal rating scale (VRS) were recorded 4-hourly at rest and with movement for 48 h. The (VRS) was interpreted by the house officer who was also blinded from the matter of study. Movement pain was defined by pain on rolling, sitting, or coughing.

Side effects were assessed by sedation score, nausea score, antiemetic use, and sleep quality score. Arterial blood pressure, heart rate, and respiratory rate data were collected. Patients were questioned daily about vivid dreams or hallucinations by the anesthesiologist who is responsible of the study.

Data were summarized as means ± standard deviation, medians and ranges, are categorized in tables. Hypothesis testing used Student's t-test for parametric data and Wilcoxon's ranked sum test for nonparametric data. $P < 0.05$ was considered statistically significant. The groups had been revealed as ketamine group and placebo group, after the data had been interpreted and analyzed.

Results

Sixty patients were randomized to the ketamine group and 60 to the control group. SAE scores were collected on 115 patients at 24 h and 109 patients at 48 h. Losses were from withdrawal of four ketamine patients and six control patients. SAE data at 48 h were missing from one patient in the control group. Patient demographic and surgical data were plotted in **table 1** as below:

A larger proportion of patients in the ketamine group reported excellent analgesia (42%) than control patients (17%) during the 0–24 h period (Table 2). At 24 h, the ketamine group was 2.5 times more likely to have a SAE score of excellent than the control group.

Table 1: Demographic and intraoperative patient's data

	Ketamine group (n=60)	Control group (n=60)
Age (year)	63±15	61±15
Gender (M/F)	37/23	39/21
Weight (kg)	83±15	85±15
ASA physical Status		
I	18	14
II	36	40
III	6	10
Smokers	7	11
Type of surgery		
General	24	31
Orthopedic	5	10
Gynecology	31	19
Duration of surgery (min)	110 (45-150)	150 (70-230)
Duration in Recovery room (min)	30 (25-45)	38 (25-85)
Added analgesics at 1st 24 hrs.	4 patients	21 patients
Added analgesics at 2nd 24 hrs	3 patients	9 patients
Dropped cases		
Uncontrolled pain	1 patient	4 patients
Hallucinations	3 patients	0
Other	0	2 missed data

Table 2: Subjective analgesia efficacy % after surgery

Subjective analgesia efficacy	Ketamine group	Control group	P
At 24 hours			0.008
Excellent =1	24 (42%)	9 (15%)	
Good =2	21 (37%)	33 (57%)	
Satisfactory =3	9 (16%)	8 (14%)	
Poor =4	3 (5%)	8 (14%)	
Total	57	58	
At 48 hours			0.7
Excellent =1	19 (33%)	18 (33%)	
Good =2	24 (43%)	20 (38%)	
Satisfactory =3	11 (22%)	14 (26%)	
Poor =4	2 (3%)	0 (0%)	
Very poor =5	0 (0%)	1 (2%)	
Total	56	53	

Pain scores (VRS) were lower at rest ($P < 0.05$) and with movement ($P < 0.05$) over 48 h (**Fig. 1**). Analgesic interventions, defined as the need to administer diclofenac sodium 75 mg I.M were more frequent in control patients (21 interventions) than ketamine patients (4 interventions) in the 0–24 h period ($P < 0.05$). The 48 h period had 9 interventions in control patients, 3 in ketamine patients ($P > 0.05$).

Median sedation scores were lower in the ketamine group during the 0–24 h period ($P < 0.05$) but identical in the 24–48 h period ($P > 0.05$). There were no significant group differences in physiological variables, nausea score, or antiemetic administration (Table 3).

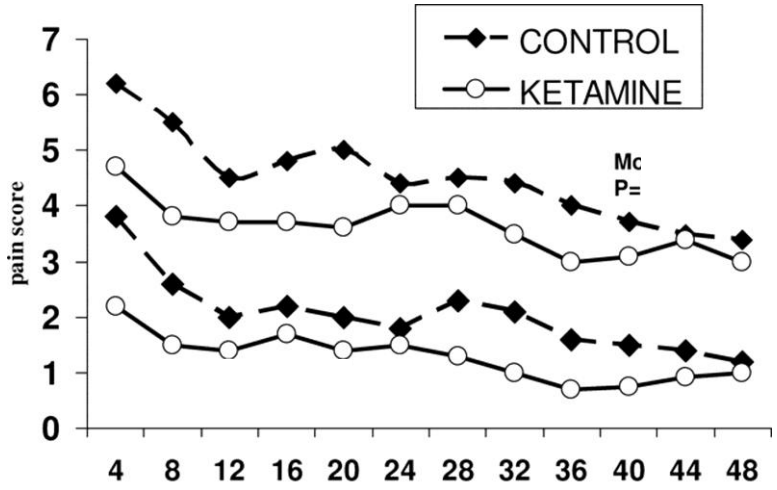

Figure 1: Repeated pain score measures at rest and movment

Table 3: Postoperative follow-up patient's data

	Ketamine group	Control group	P
Heart rate			
0-24 hrs	86±12	84±13	0.5
24-48 hrs	85±11	84±12	0.7
Systolic blood pressure			
0-24 hrs	133±17	134±18	0.8
24-48 hrs	136±20	131±17	0.1
Respiratory rate			
0-24 hrs	16±2	16±2	0.15
24-48 hrs	17±1	17±2	0.7
Sedation score			
0-24 hrs	0 (0-3)	1 (0-3)	0.08
24-48 hrs	0 (0-3)	0 (0-3)	0.1
Nausea score			
0-24 hrs	1 (0-2)	0 (0-2)	0.4
24-48 hrs	0 (0-2)	0 (0-2)	0.9
Antiemetic dose			
0-48 hrs	1	1	0.9

Psychomotor and sleep disturbance explained in (Table 4). Eleven patients experienced brief non-disturbing hallucinations, but were not withdrawn as they remained oriented. Such events were not significantly increased in the ketamine group. Three patients, all in the ketamine group, had disturbing hallucinations/confusion and were withdrawn, in spite of the hallucinations can be managed by adding a dose of diazepam (0.25 mg/kg b. wt.) intravenously. A further ketamine group patient was withdrawn because of uncontrolled pain. Control group withdrawals were due to uncontrolled pain (four patients) and missed data (two patients).

N.B. "The patient who needs more than on dose of diclofenac in 24 hours were excluded from the study and considered as uncontrolled pain".

Table 4: Psychological and sleep disturbances

	Ketamine	**Control**	**P**
Vivid dreaming 0-48 hrs.	19 (34%)	19 (35%)	0.8
Hallucinations			

Non-disturbing	6 (10%)	5 (9%)	
Disturbing (withdrawn)	3 (5%)	0 (0%)	
Sleeping quality score ≥3			
0-24 hrs	26 (46%)	30 (56%)	0.5
24-48 hrs	27 (48%)	28 (51%)	0.6

Discussion

The addition of a small-dose ketamine infusion to tramadol resulted in superior analgesia, significant analgesic-sparing, less sedation, and reduced need for physician intervention to manage pain after major surgery. The benefit from ketamine was evident throughout the 48-h study period but greatest in the first 24 h. There were similar neurocognitive side effects in the two study groups, although a few ketamine group patients were withdrawn because of disturbing hallucinations.

The study design achieved low pain scores, as patients with resting (VRS >4) were assessed and less analgesic interventions. Significantly reduced needs for such interventions in ketamine patients could be considered a stunting marker for increased analgesic efficacy. The study design was based on analgesic trials after laparotomy that also reported low pain scores [6-9] although combining ketamine and tramadol achieved better scores than morphine/ketamine [9] or morphine/tramadol. [6]

Peri-operative ketamine for acute postoperative pain has been recently reviewed. [1, 4, 5] Elia and Tramer [4] concluded that, despite many published trials, the clinical relevance of adding ketamine for postoperative analgesia remained unclear. Reported pain score reductions were modest, but the subjective analgesia efficacy (SAE) was clearly significant in ketamine group during the first postoperative 24 hours, as more ketamine patients rated analgesia as excellent, suggesting that these modest reductions in pain were clinically meaningful during the 0–24 h period.

Similar SAE scores during the 24–48 h period suggested that lower pain scores and another analgesic use had less clinical meaning. Tramadol infusion rates were based on efficacy shown in previous work. [6] Ketamine plasma levels may also have been relevant, as Owen et al. [10] found that fixed infusion rates of ketamine did not achieve constant levels in all patients, with 11/30 patients having decreasing levels with infusions running for 24 h.[10] The ketamine infusion rate was chosen, as without adverse cardiovascular or psychomemetic effects. [11, 12]

This study had shown that infusion of ketamine during the second postoperative day (24-48 hours) was unnecessary. However, prolonged analgesic benefit from single-dose ketamine was not shown after visceral surgery [16] so it would appear necessary to continue ketamine postoperatively in this patient group.

Lower pain scores in the ketamine group should be interpreted together with the significant analgesia-sparing effect. Reduced analgesic consumption may relate to the direct analgesic actions of ketamine mediated via cholinergic, μ receptors agonists, and monoaminergic mechanisms. [2].

Unlugenc et al. [7] showed, in a small trial, that ketamine-tramadol combinations achieved limited improvement in early postoperative analgesia compared with tramadol alone. Benefits from ketamine may have been blurred by larger tramadol doses, and studies indicate that PCA ketamine has lower efficacy than ketamine given by continuous infusion. [1] Ketamine trials have frequently been small and Elia and Tramer [4] reported the median number of subjects receiving ketamine in trials was only 25.

Reeves et al. [9] reported a 23% hallucination rate when administering morphine PCA after major surgery and a 33% rate when ketamine was added. The hallucination rate in this study was considerably less. Morphine had been used in the Reeves et al. study, while in this study tramadol was used. Tramadol may result in less psychomotor disturbance in the elderly than morphine. [19]

A drawback of our study was the requirement of two infusion devices to administer ketamine and tramadol in addition to the usual post operative fluid line. No administration errors occurred. Combining ketamine and tramadol in the same fluid would simplify the technique, but pharmaceutical data supporting this were not available. The drugs were combined for 24 h in a previous study. [7]The patient controlled analgesia (PCA) instruments are not available in our environment and require a good level of education and dealing with instruments by the patients in order to avoid drawbacks and abuse. The continuous post operative analgesia was more applicable in our circumstances.

Conclusion

A small-dose of ketamine infusion was a useful adjunct to a tramadol infusion after major surgery, as patients reported significantly better opinions of their analgesic medicine at 24 hours. Pain scores were lower in the ketamine group for 48 h after surgery with a significant analgesics-sparing effect.

Appendix

Pain Score (4 hourly)

Verbal rating scale (VRS): 0 (no pain) to 10 (worst imaginable pain)

Sedation Score (0–4) (4 hourly)

0 = alert, 1 = mildly drowsy/easy to arouse, 2 = frequently drowsy/easy to arouse, 3 = somnolent/difficult to arouse, 4 = asleep

Subjective Assessment of Analgesic Efficacy (1–5) (Daily)

"How effective was your medication in relieving your pain over the last 24 h?"

1 = excellent, 2 = good, 3 = satisfactory, 4 = poor, 5 = very poor

Sleep Quality (1–5) (Daily)

"What has been your quality of sleep during the past 24 h?"

1 = much better than usual, 2 = better than usual, 3 = same as usual, 4 = worse than usual, 5 = much worse than usual

References:

1-Subramaniam K, Subramaniam B, Steinbrook RA. Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. Anesth Analg 2004; 99:482–95.

2-Schmid RL, Sandler AN, Katz J. Use and efficacy of low-dose ketamine in the management of acute postoperative pain: a review of current techniques and outcomes. Pain 1999; 82:111–25.

3-Himmelseher S, Durieux ME. Ketamine for perioperative pain management. Anesthesiol 2005; 102:211–20.

4-Elia N, Tramer MR. Ketamine and postoperative pain—a quantitative systematic review of randomized trials. Pain 2005; 13:61–70.

5-Bell RF, Dahl JB, Moore RA, Kalso E. Perioperative ketamine for acute postoperative pain: a quantitative and qualitative systemic review (Cochrane Review). Acta Anaesthesiol Scand 2005; 49:1405–28.

6-Webb AR, Leong S, Myles PS, Burn SJ. The addition of a tramadol infusion to morphine patient-controlled analgesia after abdominal surgery: a double-blinded, placebo-controlled randomized trial. Anesth Analg 2002; 95:1713–18.

7-Unlugenc H, Gunduz M, Ozalevli M, Akman H. A comparative study on the analgesic effect of tramadol, tramadol plus magnesium, and tramadol plus ketamine for postoperative pain management after major abdominal surgery. Acta Anaesthesiol Scand 2002; 46:1025–30.

8-Chen Y, Chan SY, Ho PC. Isobolographic analysis of the analgesic interactions between ketamine and tramadol. J Pharm Pharmacol 2002; 54:623–31.

9-Reeves M, Lindholm DE, Myles PS, et al. Adding ketamine to morphine for patient-controlled analgesia after major abdominal surgery: a double-blinded, randomized controlled trial. Anesth Analg 2001; 93:116–20.

10-Owen H, Reekie RM, Clements JA, et al. Analgesia from morphine and ketamine. A comparison of infusions of morphine and ketamine for postoperative analgesia. Anaesthesia 1987; 42:1051–6.

11-Adriaenssens G, Vermeyen KM, Hoffmann VL, et al. Postoperative analgesia with i.v. patient-controlled morphine: effect of adding ketamine. Br J Anaesth 1999; 83:393–6.

12-Stubhaug A, Breivik H, Eide PK, et al. Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. Acta Anaesthesiol Scand 1997; 41:1124–32.

13-Menigaux C, Fletcher D, Dupont X, et al. The benefits of intraoperative small-dose ketamine on postoperative pain after anterior cruciate ligament repair. Anesth Analg 2000; 90:129–35.

14-Suzuki M, Tsueda K, Lansing PS, et al. Small-dose Ketamine enhances morphine induced analgesia after outpatient's surgery. Anesth Analg 1999; 89:98–103.

15-Weinbroum AA. A single small dose of postoperative ketamine provides rapid and sustained improvement in morphine analgesia in the presence of morphine- resistant pain. Anaesth Analg 2003; 96:789–95.

16-Dahl V, Ernoe PE, Steen T, et al. Does ketamine have preemptive effects in women undergoing abdominal hysterectomy procedures? Anesth Analg 2000; 90:1419–22.

17-Joly V, Richebe P, Guignard B, et al. Remifentanil-induced postoperative hyperalgesia and its prevention with small dose ketamine. Anesthesiol 2005; 103:147–55.

18-Apfelbaum JL, Gan TJ, Zhao S, et al. Reliability and validity of the perioperative opioid-related symptom distress scale. Anesth Analg 2004; 99:699–709.

19-Aubrun F. Management of postoperative analgesia in elderly patients. Reg Anesth Pain Med 2005; 30:363–79.

20-Creekmore FM, Lugo RA, Weiland KJ. Postoperative opiate analgesia requirements of smokers and nonsmokers. Ann Pharmacother 2004; 38:949–53.

Clinical Sciences, Anesthesiology
Assistant lecturer, Department of surgery, College of Medicine,
Al Mustansiriya University, Baghdad, Iraq.
Lecturer in Anesthesiology, Department of Surgery, College of Medicine,
Al Mustansiriya University, Baghdad, Iraq